Structure
Previews

Docking Peptides on Proteins: How to Open a Lock, in the Dark, with a Flexible Key

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In this issue of *Structure*, Schindler et al. (2015b) present us with pepATTRACT, a protocol embedded in the ATTRACT docking engine for fully blind flexible peptide docking on proteins that yields high quality models of complexes.

Peptide-protein interactions are ubiquitous in the cell and play a central role in numerous biological processes. As such they represent key systems in a drug-design perspective and one current strategy is to produce peptides whose sequence has been extracted from a known protein partner of a specifically targeted protein (London et al., 2013).

To obtain the structure of the resulting peptide-protein complex in the case of incomplete experimental data, one can resort to computational docking methods. These were originally developed to determining the geometry of small drugs in protein binding sites or the structure of protein-protein complexes. The protein partners were then expected to remain essentially rigid while binding, thus following the classic "lock and key" model. The flexibility of small molecule drugs was generally taken into account, but this involves only few degrees of freedom. Further implementations in protein-protein docking approaches took into account the conformational variation of the partner proteins upon binding ("induced fit"), but only in a marginal way by modeling side-chain flexibility or even flexible loops on the protein surfaces or locally restricted global movements of the proteins. The global shape and secondary structure of the binding partners would nonetheless be conserved during the docking process.

The binding of a peptidic fragment on a protein, however, introduces a new challenge in the field. Protein-peptide interfaces are comparable to protein-protein interfaces, with a generally smaller size and more hydrophobic character (London et al., 2010). Peptidic fragments, though, can span a large conformational space; most of them will not retain their original structure when they are extracted from a native protein matrix. In this perspective, a fully flexible treatment of the peptide appears to be necessary but will lead to a considerable increase in the computational cost of the docked structures. This increase has been previously compensated for by using local docking approaches in which experimental information regarding the peptide binding site can be used to restrict the ligand conformational search around the protein surface (Raveh et al., 2011; Trellet et al., 2013). Such information however is not always available, and a search involving the whole protein surface is often necessary.

From this standpoint, the pepATTRACT protocol presented by Schindler et al. (2015b) follows a three-step sequence for performing fully blind and flexible peptide docking on a protein: (1) the generation of three peptide models from the sequence (Trellet et al., 2013); (2) a coarse-grained, rigid body docking procedure; (3) and finally, a flexible interface refinement using the iATTRACT method (Schindler et al., 2015a).

The protocol can be tested via a dedicated web interface (http://www.attract.ph.tum.de/services/ATTRACT/peptide.html) that sets up scripts for the rigid body sampling and interface refinements stages. Running the complete protocol on a standard complex (including a final MD refinement of the best 1000 models) will take around 16 hr on a standard desktop PC, thus making pepATTRACT an efficient and accessible tool for the study of peptide-protein complexes.

This protocol, which requires no prior knowledge of the docked peptide conformation, or of its binding site, was tested on 80 peptide-protein complexes and yielded high quality models for 70% of the complexes, which is comparable to state-of the art docking protocols such as Rosetta FlexPepDock (Raveh et al., 2011) or HADDOCK (Trellet et al., 2013). Introducing restraints regarding the peptide binding site on the protein, i.e., performing local docking simulations, further increased the quality of the results. This performance opens prospects for the use of computer programs for high-throughput protein-peptide docking in the search for new peptide drugs.

Remarkably, pepATTRACT also performs well for binding site prediction (i.e., interface post prediction). As shown in earlier protein-protein docking studies, the contact analysis of docking models can be used to predict the proteins interface residues. Similar results were obtained with pepATTRACT, which could predict the position of the peptide binding site regardless of the peptide conformation. This result is of particular interest to us because it concurs with the observations made during a recent study of the binding of an anti-tumoral peptide (NFL-TBS.40.63) on tubulin (Laurin et al., 2015), in which the various structures that had been generated for the peptide would all preferably dock on the same specific binding site on the tubulin surface. In the case of the NFL-TBS.40.63 peptide, the binding site on tubulin turned out to be structure independent but

sequence specific, because disrupting the peptide sequence (while maintaining its amino-acids composition) would lead to a different docking pattern on the protein surface. In this perspective, running the pepATTRACT protocol with the original 80 peptide-protein complex benchmark, but using this time scrambled peptides sequences, would be of interest in determining whether the original peptide binding sites found in the present study are conserved.

Furthermore, the results from pepATTRACT and our study on the NFL peptide bring a new hint to classical issues addressed while working on peptide-protein interactions; namely, how do peptides compensate for the configurational entropy lost upon binding or what is the recognition process for these binding events (London et al., 2010)? It might be that for some flexible peptides, having many of their conformations able to bind in a favorable manner onto a restricted area on the protein surface permits the conservation of a high level of entropy along most of the association pathway. This may assist the recognition process by keeping the peptide in the binding site long enough for a large array of specific protein-peptide interactions to eventually form and thus enhancing the binding kinetics in a way analogous to the "fly-casting" effect (Shoemaker et al., 2000) that was evidenced in the case of the association between disordered and globular proteins (Sugase et al., 2007).

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